

REMARKS

Reconsideration is requested.

The specification and figures have been amended above to include a third sheet of Figure 2 which was included with the originally-filed PCT application (PCT/EP93/03325), from which the present application claims benefit. See, the attached copy of 17 sheets of drawings from the published PCT application (WO 94/12670).

The present application claims benefit of intermediate applications Serial Nos. 09/378,900 and 09/044,665, which issued as U.S. Patent Nos. 6,495,670 and 6,051,696, respectively. Each of these applications fails to include the additional sheet of Figure 2 (i.e., Figure 2B in the attached revised figures).

The parent PCT application (i.e., PCT/EP93/03325) was filed with a complete set of drawings.

The U.S. national phase of the PCT application (i.e., Serial No. 08/256,568) was also filed with a complete set of drawings. See, the attached excerpt from the Patent Office copy of the file history of Serial No. 08/256,568, as well as the file jacket from the same indicating that 17 sheets of drawings were filed.

A review of the file history of the parent application Serial No. 08/256,568, suggest however that once formal drawings were filed prior to issuance of the parent U.S. Patent No. 5,846,704, the second of three sheets of Figure 2 was omitted. U.S. Patent No. 5,846,704, therefore also does not include, as issued, a complete set of figures.

The application which issued as parent U.S. Patent No. 6,495,670 and 6,051,696, were apparently filed with the set of drawings used for formal purposes or based on the figures used for formal purposes in the parent application which issued as U.S. Patent No. 5,846,704. This apparent inadvertent error has only recently been appreciated and the applicants are moving to request correction of the parent patents separately.

Inclusion of the missing sheet of Figure 2 is not believed to add new matter. The Examiner is requested to consider the following in this regard.

Figure 2, as originally-filed in the PCT application, and attached, includes an alignment of the 5' UR nucleotide sequences of isolates from four types of HCV. See, page 29, lines 13-15 of the specification.

The specification teaches that Figure 2 includes nucleotides in the region from -291 through -55 such that the sequences shown in the attached sheet Figure 2B would be expected to be included. See, page 38, lines 28-29 of the specification.

The third sheet of Figure 2, which was filed as FIG. 2B with the Response of April 19, 2002 and the originally-filed application (attached hereto as redesignated Figure 2C), describes all of the isolates included in the attached additional sheet Figure 2B. Moreover, the sequences shown in the additional sheet Figure 2B attached are direct continuations of the 5' UR region of the sequences (i.e., continuing from positions -147 through -219).

The sequences in the regions described in the additional sheet Figure 2B are moreover referred to in the specification and/or were publicly available at the time the present application was filed.

Specifically, the applicants note that the isolates HCV1, HCVJ, HCVJ6, HCVJ8 and BR56 were deposited and are available through Accession Nos. M62321, D10749, D00944, D01221 and D13348, respectively, as described, for example, on page 30, lines 1-16 and page 35, lines 4-5 of the specification. The sequences of isolates BU74 and BU79 are available through Accession Nos. D13449 and D13450, respectively, as disclosed at page 35, lines 5-6 of the specification. The sequence of isolate E-b8 is available through Accession No. D10116 and is identifiable through a search of Genbank. The sequence of isolate Z6 is described, for example, in Bukh et al. (1992 PNAS 89:4942-4946). See, page 38, lines 18-19 of the specification. Finally, the sequences of GB80 and GB81 are available through deposit Accession Nos. D13451 and D13452, respectively, as disclosed on page 35, lines 6-8 of the specification. Many of these sequences are further described and available in Chan et al. (Journal of General Virology (1992), 73, 1131-1141), of record.

Further support for the additional sheet of drawings may be found, for example, on page 9, lines 3-4 of the specification wherein a region extending from nucleotide position -170 to nucleotide position -155 is indicated as being contained in Figure 2. Moreover, the specification describes that Figure 2 contains a conserved region between -220 and -180. See, page 30, lines 14-15 of the specification. This conserved region is shown in the additional sheet of Figure 2 attached as Figure 2B.

The boxed regions in the attached Figure 2B extending from position -170 to position -155 and the corresponding SEQ ID NOs:5, 13 and 17 are described, for example, on pages 9-11 and specifically page 11, lines 15-32 of the specification. The

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boxed region and SEQ ID NO:27 in the attached sheet Figure 2B is also described on page 10 of the originally-filed application.

No new matter has been added. Entry of the attached three sheets of Figure 2 in place of the previously filed two sheets of Figure 2 is requested.

Claims 24-27 are pending. Claims 26 and 27 have been withdrawn from consideration. Claim 25 has been allowed.

The Section 102 and alternative Section 103 rejections of claim 24 as allegedly being anticipated and/or obvious over Sommer (Nucleic Acids Researched, Vol. 17, No. 18 (1989)), are traversed. Reconsideration and withdrawal of the rejections are requested in view of the following distinguishing comments.

The presently claimed invention provides, in claim 24, an isolated polynucleic acid specifically hybridizing with a sequence selected from a group consisting of SEQ ID NO:55 to SEQ ID NO:81, under conditions allowing discrimination of up to 1 nucleotide mismatch, or the complement thereof. The Examiner asserts that Sommer teaches that "all that is required for specific priming (i.e., hybridization) is a sequence of 5'-TAG-3'. Note that each of SEQ ID NOs:55-81 comprise the a [sic] sequence 5'-TAG-3' at nucleotide positions 44-46." The Examiner concludes that "it could be said that Sommer et al. teach an isolated polynucleic acid which will specifically hybridize with any of SEQ ID NOs:55 – SEQ ID NO:81 or the complement thereof under conditions allowing discrimination of up to 1 nucleotide mismatch." See, pages 3-4 of the Office Action dated July 25, 2003 (Paper No. "072303", as identified by the Examiner on page 1 of the Office Action).

While "it can be said" that Sommer teaches as much as the Examiner believes, the same would not be the interpretation of one of ordinary skill in the art. Specifically, while Sommer may teach that "primers with a length between 17-20 nt need at least three homologous nucleotides at their 3' end for successful priming", and "primers to be employed in claiming homologous genes [should have the following criteria] the length should be preferably between 20-24 nt and the 3' nucleotides should match completely" Sommer does not teach that this is all that is required, as apparently interpreted by the Examiner. In fact, as explained below, the applicants believe the specific priming described by Sommer, which the Examiner equates to hybridization, is determined by a combination of overall percent identity of the primer with the target sequence and perhaps the number of 3' nucleotides of the primer which exactly match the target sequence.

Specifically, the following Table summarizes the information from Table 1 of Sommer and details, for each primer the length of the primer, the number of 3' nucleotides of the primer which exactly match the target sequence, the overall percent identity of the primer with the target sequence and the "amplification efficiency" as indicated by Sommer.

| Primer | Length (nts) | No of 3' nts of primer exactly matching target sequence | Overall % identity of primer with target sequence | Amplification efficiency |
|--------|--------------|---|---|--------------------------|
| a | 17 | 0 | 82 | - |
| b | 17 | 0 | 82 | - |
| c | 17 | 3 | 47 | + |
| d | 17 | 4 | 47 | + |
| e | 17 | 1 | 76 | - |
| f | 17 | 2 | 76 | - |
| g | 17 | 3 | 71 | ++ |
| h | 17 | 9 | 65 | ++ |
| i | 17 | 6 | 59 | + |
| k | 17 | 3 | 53 | + |
| l | 17 | 8 | 88 | ++ |
| m | 20 | 2 | 70 | - |
| n | 36 | 2 | 61 | + |

The following will be appreciated from the above.

Primer "n" has only 2 nts at its 3' end that are exactly matching the target sequence and yet the amplification efficiency of primer n is rated "+". Primer "n" is more than the 17-20 nt long primer which is specifically mentioned by Sommer. Moreover, primer "n" is 61% identical with the target sequence of 36 nucleotides. Accordingly, Sommer's conclusions, if valid for primers of 17-20 nt, which the applicants do not believe to be true, are not applicable to primers of greater (or lesser) length.

Primers c, g, and k (all 17 nts in length) all have 3 nts at their 3' end that are exactly matching the target sequence. Yet, there is a marked difference between amplification efficiency with primer g (rated "++") and primers c and k (both rated "+"). There must thus be additional elements or factors (other than three 3' exactly matching nts) contributing to the hybridization efficiency of a probe/primer to its target sequence.

One such element is likely the overall % identity of a probe/primer with its target sequence: for primer g this is 71%, while for primers c and k these are 47% and 53%, respectively. Thus, the higher the overall % identity for the otherwise "identical" probes/primers (identical for length and for having 3 exactly matching 3'nts), the greater the specificity of hybridization of said probe/primer with its target sequence. More is therefore required than merely a 3 nt 3' match for even primers of 17-20 nts.

Following the overly broad interpretation of the Examiner of Sommer et al. 1989, i.e., that only 3 exactly matching 3'nts are sufficient for specific hybridization of a probe/primer with its target sequence, the Examiner would presumably expect that greater hybridization specificity would be obtained if more 3'nts exactly match with the target sequence were included in the primer. The following two examples are, however, in contradiction with this expectation:

- Primers d and i (having 4 and 6 exactly matching 3'nts, respectively) perform less well than primer g (having 3 exactly matching 3'nts). Note that the overall % identity of primers d and i to their target sequence (47% and 59%, respectively) is lower than the % identity of primer g to its target sequence (71%), see also comments above with regard to primers c, g and k.
- Primers h and l apparently are the only primers of Sommer et al. performing as well as primer g but these primers have 9 and 8 exactly matching 3'nts, respectively. This is thus by far exceeding the minimum requirement of 3 exactly matching 3'nts of primer g.

It thus appears that primer g is an exception rather than the rule and the Examiner's interpretation (i.e., that only three 3' nts are required) of Sommer's conclusions (i.e., that at least three 3' nts are required) is in error.

Further, following the broad interpretation of the Examiner of Sommer et al. 1989, i.e., that only 3 exactly matching 3'nts in a probe/primer are sufficient for specific hybridization of that probe/primer to its target sequenced, one would expect, incorrectly, that the overall % identity of any (emphasis added) probe/primer to its target sequence would have to be only between 8% (3/36 for active primer n of Sommer et al.; note that this should in fact be 6%, i.e., 2/36, see comments above with regard to primer "n") and 18% (3/17). None of the primers of Sommer et al., however, do not fulfill this requirement as the minimum % identity of an active primer of Sommer with at least 3 exactly matching 3'nts is 47% (see primer c).

The Examiner's interpretation of Sommer and application of the same to reject claim 24 as being unpatentable is, with due respect, unfounded. The rejections of claim 24 over Sommer should be withdrawn.

For completeness, the applicants note that the Examiner states in ¶7 on page 4 of Paper No. "072303" that the "pending claims must be given their broadest reasonable interpretation consistent with the specification". The Examiner appears however to have broadly and inappropriately interpreted Sommer et al. and ignored the present specification completely. In fact, the remarks of the Amendment filed March 26, 2003 provided a specific interpretation of the claim based on the specification.

Withdrawal of the Section 102 and Section 103 rejections of claim 24 is requested.

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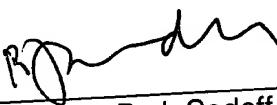
The obviousness-type double patenting rejection of claim 24 over claim 7 of U.S. Patent No. 6,495,670, is traversed. Reconsideration and withdrawal of the obviousness-type double patenting rejection of claim 24 is requested as the same appears to be based on the inappropriate interpretation of claim 24 as was discussed above with regard to the rejection of claim 24 over Sommer. Consideration and withdrawal of the rejection are requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

The Examiner is requested to contact the undersigned if anything further is required in this regard.

Respectfully submitted,

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IN THE SPECIFICATION

Amend the specification as follows.

Page 29, delete the paragraph at line 13 and insert the following therefore:

Figure 2 Figures 2A-2C

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IN THE FIGURES

Amend the figures as follows.

Insert the attached Figures 2A-2C in place of FIG. 2A and FIG. 2B filed with the

Response dated April 19, 2002.